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APPLICATION NO.	FILING DATE	FIRST-NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,035	11/19/99	ENIKOLOPIAN G	

HM22/1004

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EXAMINER
SCHNIZER, R

ART UNIT	PAPER NUMBER
	13

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/444,335	Applicant(s) Enikolopov et al
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Sep 11, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-50* is/are pending in the applicat

Of the above, claim(s) *25-50* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

An amendment was received and entered as Paper No. 12 on 9/11/00. Applicant's election with traverse of group I, claims 1-89, 17, and 22-24 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the claims of groups I-VII are neither independent nor distinct. More particularly, Applicant argues that the all claims define the same essential characteristic of a single disclosed embodiment of an invention, *i.e.* DNA comprising a regulatory sequence of a mammalian nestin and a gene encoding a fluorescent protein. This is not found persuasive because a nestin regulatory sequence linked to a reporter gene can be used for a variety of different purposes which are patentably distinct as shown by their separate classifications. Applicant argues further that the searches required for the various inventions are overlapping. This may be true, however, the searches are not coextensive. That is, a search of any one of the classes does not encompass any of the other classes in its entirety. With regard to groups VI and VII, Applicant notes that these groups are classified identically. However, restriction is still proper because the inventions are distinct methods with distinct steps which measure unrelated outcomes, thus the required searches would be non-coextensive.

After further consideration, groups II, III, and IV are rejoined with group I, so that the invention under consideration comprises transgenic animals, constructs for their construction, a method of making the animals, and a first method of using the animals.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-50 are withdrawn from consideration by the examiner. Claims 1-24 are under consideration in this office action.

Double Patenting

Applicant is advised that should claims 1, 6, 7, and 8 be found allowable, claims 17, 22, 23, and 24 will be objected to under 37 CFR 1.75 as being a substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 17 is a product by process claim in which the product is identical to that of claim 1. Further, the mammals of claims 22, 23, and 24 are identical to the mammals of claims 6, 7, and 8, respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic mice comprising a nestin regulatory sequence, does not reasonably provide enablement for any non-mouse transgenic animals comprising a

nestin regulatory sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention encompasses nonhuman transgenic mammals which have integrated into their genome a DNA comprising a regulatory sequence of a mammalian nestin gene operably linked to a gene coding for a fluorescent protein. The fluorescent protein must be expressed in multipotent stem cells and progenitor cells of the transgenic mammal.

It is well known in the art that the production of transgenic animals with desired characteristics is highly unpredictable. As of the effective filing date of the claimed invention only a limited number of species of transgenic animals had been produced. There is no evidence which supports that transgenic animals from all species possessing the desired phenotype can be readily produced without undue experimentation. It is also well known in the art that the expression of a transgene and the effects of its expression on the animal as a whole are not predictable due to numerous uncontrollable factors such as the site of integration and methylation-inactivation of the transgene. See Kappel et al., the right column of page 549, for example.

With respect to the DNA construct of required to make the animals, the specification is not enabling for the use of all combinations of nestin regulatory sequences and fluorescent proteins. It is well known in the art that the level and the specificity of expression of a transgene as well as the phenotype of the transgenic animal thus produced are greatly dependent of the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding or

non-coding sequences present in the transgene construct, the site of integration, etc., are all important factors in controlling the expression of a transgene. The specification does not provide sufficient guidance on how to isolate, select and screen for DNA constructs comprising all nestin regulatory sequences from all mammals which would be suitable for producing transgenic mammals with the desired phenotype and utility. Accordingly, in view of the unpredictability of the art and the lack of guidance provided by the specification, it would have required undue experimentation to prepare DNA constructs which utilize all nestin regulatory sequences and to produce transgenic animals from all mammalian species which express the constructs.

Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Additionally, Kappel et al.(Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). The level of skill in the transgenic art is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. Mullins teaches that position effects can cause loss of cell specificity of expression, overexpression, or silencing of the transgene, and that a given construct may react very differently from one animal to another. See page S37, lines 7-12, and page S39, first sentence of last paragraph. Furthermore, Ebert et al. (Molecular Endocrinology, 1988) disclose the production of transgenic mice expressing human somatotropin regulated by the

mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2). Hammer et al. (Journal of Animal Science, 1986) disclose the production of transgenic mice, sheep and pigs; however only mice exhibited an increase in growth due to the expression of human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). Thus, with respect to the unpredictability of transgene expression levels sufficient to confer a particular phenotype due to species differences and/or specific elements within a transgene construct, it would have required an undue amount of experimentation to extend the results obtained in mice to levels of transgene product in any and all non-human transgenic mammals expressing transgenes encoding any and all fluorescent proteins, the consequences of that production, and therefore, the resulting phenotype.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17 and 19-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman et al (Neuron 12(1): 11-24, 1/1994), as evidenced by Hogan et al (Manipulating the

Mouse Embryo: A Laboratory Manual (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory, 1986).

Zimmermann teaches transgenic mice comprising a lac-Z transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. See entire document, especially Abstract; Table 1, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph. It is noted that Lac-Z encodes beta-galactosidase which comprises 38 tryptophan residues, and is therefore a fluorescent protein. See enclosed sequence. The mice were made as instructed by Hogan, *i.e.* by microinjection of recombinant expression constructs into the pronuclei of fertilized mouse eggs. See sentence bridging pages 153 and 154; and pages 157-173 of Hogan.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (Neuron 12(1): 11-24, 1/1994) in view of Chiochetti et al (Bichim. Biophys. Acta 1352(2): 193-202, 5/1997).

Zimmermann teaches transgenic mice comprising a construct containing a *lac Z* reporter transgene under the control of the promoter and second intron enhancer of the rat nestin gene. Beta galactosidase was expressed in neuronal stem cells of the resulting animals, and allowed measurement of these cells. See entire document, especially Abstract; Table 1, pages 12, 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph.

Zimmerman does not teach a construct comprising green fluorescent protein.

Chiochetti teaches the use of green fluorescent protein as a reporter gene, in lieu of *lac Z*, for use in transgenic animals.

It would have been obvious to one of skill in the art at the time of the invention to substitute the green fluorescent protein coding sequence of Chiochetti for *lac Z* in the construct of Zimmerman. One would have been motivated to do so because Chiochetti teaches that green fluorescent protein is a more powerful and sensitive tool for studying gene expression than is lac Z. See abstract, and page 202, column 1, lines 5-7.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM

and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Karen M. Hauda

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Richard Schnizer, Ph. D.